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Placental characteristics and complications in monochorionic twin pregnancies

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Citation

Zhao, D. P. (2016, November 8). *Placental characteristics and complications in monochorionic twin pregnancies*. Retrieved from <https://hdl.handle.net/1887/44230>

Version: Not Applicable (or Unknown)

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Issue Date: 2016-11-08

Future Perspectives

Although postnatal examination of monochorionic (MC) placentas using color dye injection have shed more light on the pathophysiology of various disorders in MC twins, the examination is usually performed by visual inspection, and is time-consuming and prone to interobserver variation. In addition, the *in vitro* nature of postnatal examination of MC placentas limits the extrapolation of the findings into evaluation of *in vivo* scenarios.

This chapter focuses on various proposals for research directions to further improve our understanding of the pathophysiology of disorders in MC twins. Improved knowledge on the various aspects and characteristics of MC placentas may also help optimize the prenatal management and intrauterine therapy.

A. Monochorionic placenta: analysis and characteristics

1. Development of computerized methods for placental analysis

To minimize interobserver variation and diminish the time used for placental analysis, a dedicated software program may be useful to perform various measurements of placental morphology. For example, the distribution of chorionic vasculature is categorized grossly as disperse, magistral or mixed by visual inspection and is related to the donor and recipient status in TTTS.[1] In singletons, chorionic vasculature patterns are associated with placental insufficiency and fetal growth.[2] **Computerized analysis** would be useful to define the type of chorionic vasculature patterns based on objective parameters such as density of chorionic vessels and number of vascular branches, enabling subsequent investigations on the clinical consequences of chorionic vasculature patterns and differences between donor and recipient placental angioarchitecture.

2. Prenatal evaluation of placental angioarchitecture

Perinatal risk of MC twins is strongly related to the placental anomalies such as vascular anastomoses, velamentous cord insertion (VCI) and unequal placental share.[3] As a result, prenatal detection of placental anomalies could be beneficial to the risk evaluation in MC twins. Prenatal ultrasound is already a reliable tool to detect the presence of VCI or other abnormalities of cord insertion.[4] VCI is suggestive of smaller placental share and is an independent risk factor for growth discordance and fetal demise.[5] In addition, distance between cord insertions can be measured during ultrasound examination, allowing the detection of proximate cord insertions (PCIs). This may enable the investigation of **correlation between PCIs and clinical outcomes, including fetal demise.**

Detection of the different types of anastomoses and evaluation individual placental share with prenatal ultrasound examination is more difficult if not extremely challenging and not yet reliable. Werner et al. recently reported a preliminary method to identify the vascular equator using ultrasound and resonance magnetic imaging (MRI).[6] Individual placental share may be evaluated based on the combination of **identifying vascular equator with contouring the placental edge.** Although arterio-venous (AV) anastomoses and veno-venous (VV) anastomoses cannot yet be detected with prenatal Doppler ultrasound, reliable detection of arterio-arterial (AA) anastomoses during ultrasound examination has been reported.[7] AA anastomoses carry bidirectional blood flow and can compensate for a wide range of net cross-sectional area of AV anastomoses, preventing the development of TTTS and TAPS.[8] A prospective study is needed to evaluate the predictive value of the combination of **prenatal detection of VCI and AA anastomoses** in relation to the perinatal outcome of MC twins.

B. Placental characteristics in relation to specific complications: Twin–twin transfusion syndrome and Twin anemia–polycythemia sequence

1. Twin-twin transfusion syndrome

Since the majority of TTTS cases are now treated with fetoscopic laser ablation of vascular anastomoses, evaluation of the various types of anastomotic patterns on the placenta after delivery is not possible. However, color dye injection to detect residual anastomoses remains a crucial tool for **quality control**, for the evaluation of the **learning curve** of fetal surgeons and serves as an important **teaching tool** for all perinatologists involved in the care of MC twins.

Although the rate of residual anastomoses and associated post-laser TAPS or recurrent TTTS is reduced due to the application of Solomon technique for laser surgery, residual anastomoses are reported to be detected in up to 20% lasered TTTS placentas in the Solomon trial.[9, 10] With increased familiarity and experience with the Solomon technique, , we expect a decrease in the rate of residual anastomoses in the future. Large, preferably multicenter studies are required to evaluate the inter-individual, intra-individual and inter-center differences in prevalence of residual anastomoses after laser surgery using Solomon technique. Importantly, factors such as localization of the placenta (anterior or posterior), TTTS stage at operation and experience level of the fetal surgeons must be taken into account. Evidently, comparisons of the rate of residual anastomoses between the various fetal centers and between operators can only reliably be performed if placental examination is done adequately and accurately using color dye injection. Evaluation of post-laser placentas using only air injection should not be considered as a valid tool for the detection of residual anastomoses (in particular for the detection of minuscule

anastomoses).[11] Similarly, examination of post-laser placentas performed by inexperienced injectors will also lead to a higher rate of false-negative results.

Fetoscopy also provides the possibility to record the placental angioarchitecture *in vivo*. In a study from Eschbach et al., the authors found that the presence of AA anastomoses detected during fetoscopy was associated with the death in donor twin while the absence of AV anastomoses directed from recipient to donor twin was related to death in recipient twin after laser surgery.[12] In addition, the presence of VV anastomoses is related to the development of TTTS.[13-15] However, the **predictive value of VV anastomoses** in relation to clinical outcome after laser surgery is unclear. This may be due to the limited reliability of detection of vascular anastomoses by fetoscopy.

In the majority of TTTS cases managed with fetoscopic laser surgery, functional dichorionicity can be reached,[10] and post-laser fetal growth is therefore mainly dependent on the individual placental territory. However, the current fetoscopy operation instrument does not include a measurement component to objectively quantify the individual placental territory. Quintero et al. recently reported the feasibility of visible light spectroscopy to identify individual anastomoses and differentiate the individual placental territory of recipient and donor before laser ablation based on the measurement of oxygenation.[16] Further studies are required to evaluate the feasibility and accuracy of this method to define the types of vascular anastomoses and individual placental territory, and subsequently to assess their predictive value for clinical outcome after laser surgery.

2. Twin anemia polycythemia sequence

TAPS is a newly-described form of chronic intertwin transfusion occurring in 5% of MC twins.[17, 18] Due to the rarity of this disorder, previous studies on the characteristics of

TAPS placenta were often limited by the small sample size. The correlation between the **pathogenesis of TAPS and placental angioarchitecture** (including types of cord insertion, unequal placental share) remains to be elucidate, ideally, in prospective multicenter studies with large sample size. In addition, prenatal *in vivo* evaluation of placental characteristics may be also useful for the prediction of clinical outcome in TAPS. Given the miniscule nature of vascular anastomoses in typical TAPS placentas, future studies should probably focus on prenatal evaluation of the difference in color of each individual placental territory rather than on the type of anastomoses. Interestingly, ultrasound examination is already useful in detecting a difference in echodensity and thickness between the placental territory of the anemic and polycythemic twin in a part of TAPS.[18] Further investigation is warranted to show the average **difference in echodensity** between the placental territory of the anemic and polycythemic in general population of TAPS and to assess the feasibility of this difference to define individual placental share.

Recently, we proposed the color difference of the maternal side as an additional criterion for the postnatal diagnosis of TAPS and differential diagnosis between TAPS and acute peripartum TTTS.[19] However, the color difference on maternal side was measured in only 19 TAPS placentas without classification of spontaneous TAPS or post-laser TAPS. The applicability of **color difference on maternal side** to diagnose TAPS should be assessed in larger studies and in studies including cases with acute peripartum TTTS.

3. Selective intrauterine growth restriction

Selective intrauterine growth restriction (sIUGR) is a severe disorder occurring in 10% of MC twins and results from unequal placental sharing.[20, 21] In the majority of previous studies, unequal placental share is empirically defined as a placental share discordance of $\geq 20\%$.

However, a scientific definition of unequal placental share has not yet been reported and is urgently needed. The optimal method to determine the threshold of unequal placental share that significantly increase adversity of perinatal outcome is to use placental share difference as continuous variable and assess its correlation with outcome parameters.

In addition to unequal placental sharing, sIUGR placentas are also characterized by an increased incidence of VCI and large AA anastomoses.[22, 23] Prenatal detection of the combination of these three factors may help distinguish sIUGR twins from other MC twins and **classify the various types of sIUGR**, in relation to the Gratacos staging.[24]

C. Fetal inflammatory response syndrome after fetal interventions

With the improvement of survival rate after fetoscopic laser surgery for TTTS, attention is shifting towards survival without long-term morbidity. Unfortunately, post-laser complications such as preterm prelabour rupture of membranes (PPROM) and intrauterine inflammation, remain a challenge in management of TTTS.[10, 25, 26] Both PPRM and intrauterine inflammation (including clinical or histological chorioamnionitis) are associated with premature delivery and adverse short- and long-term outcome.[27, 28] Recent studies show that the risk of adverse outcome is higher in chorioamnionitis with fetal involvement, termed as fetal inflammatory response syndrome (FIRS).[29] Although funisitis is the histologic indication of FIRS, an elevated concentration of interleukin-6 (IL-6, >11 pg/mL) in fetal plasma is the crucial diagnostic criterion for FIRS.[29] The invasive nature of fetal interventions for TTTS or feticide predisposes the fetus to intrauterine infection and secondary inflammatory response. In addition, iatrogenic necrosis after fetal interventions may result in 'sterile inflammation' without the presence of microbe in amniotic sac.[30] Importantly, postmortem involution due to fetal demise after fetal interventions may

prevent the diagnosis of intrauterine inflammation based on the histologic evaluation of placenta. The **measurement of IL-6 in fetal plasma** enables the detection of severe intrauterine inflammation in all liveborns. Interestingly, Kunze et al. recently reported the feasibility of measurement of IL-6 in amniotic fluid collected noninvasively after PPROM.[31] Since PPROM occurs in around 30% after fetoscopic laser surgery or 20% after fetocide,[10, 25, 32] this method may be promising for **prenatal detection of FIRS after fetal intervention**.

In conclusion, advances in prenatal ultrasound examination and invasive fetal therapy not only provide an opportunity to improve perinatal survival rate in complicated MC twins, but also to understand the pathophysiology of the various fetal disorders and to build prediction models based on *in vivo* variables obtained prenatally.

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